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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,720	03/03/2004	Shinn-Chih Wu	WUSH3012/EM	2654

23364 7590 10/05/2004

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EXAMINER	
ALONZO, NORMA LYN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,720	WU ET AL.	
	Examiner	Art Unit	
	Norma C Alonzo	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 03 March 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-27 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for producing a transgenic swine whose somatic and germ cells comprise a transgene wherein said method comprises: (i) introducing (a) a plasmid comprising two transgenes, wherein said transgenes comprise DNA sequences encoding human clotting factor IX (hFIX) and porcine lactoferrin, respectively, wherein both transgenes are operably linked to a mammary gland specific promoter or (b) a 1:1 mixture of plasmids, one comprising a mammary gland specific promoter operably linked to a nucleic acid encoding hFIX, the other comprising a mammary specific promoter operably linked to a nucleic acid encoding porcine lactoferrin into a swine embryo, (ii) transplanting said embryo comprising said plasmid or plasmids into a pseudopregnant swine, (iii) allowing the embryo to develop into a transgenic swine, wherein expression of said transgenes result in the production and secretion of hFIX and porcine lactoferrin in the mammary tissue of said swine, wherein

the expression of recombinant porcine lactoferrin in said milk acts as an immune modulator in said swine; and said method further comprising collecting milk from said transgenic swine, does not reasonably provide enablement for producing any transgenic non-human mammal comprising (i) introducing a plasmid comprising transgenes that encode any combination of more than one protein operably linked to any promoter or (ii) introducing a 1:1 mixture of multiple plasmids that comprise a transgene having DNA sequences, encoding any different proteins operably linked to any promoter, wherein expression of said transgenes in said transgenic animal results in immunoprotection of offspring, and wherein said method further comprises isolating multiple recombinant proteins from milk of sand transgenic animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858

F.2d 731, 737, 8 USPQ2d 1400 , 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses a method for expressing multiple proteins in the milk of any transgenic non-human animal comprising microinjecting a plasmid comprising multiple transgenes encoding multiple proteins into a non-human mammalian embryo or comprising microinjecting multiple plasmids each comprising a transgene encoding different recombinant proteins into any non-human mammalian embryo. While the production of recombinant protein in milk is well known in the art, the nature of the invention of the instant application relates to the production of multliple recombinant proteins in milk whether by the use of multiple plasmids having trangenes encoding individual proteins or by the use of a single plasmid having multiple transgenes each encoding a different proteins.

As the current state of general transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations. The variation in expression levels between different cell lines and species

may be attributed to host genetic background, the site of chromosomal insertion and absence of specific transcription factors. Cameron (Cameron ER Molecular Biotechnology 7:253-276, 1997) noted, "Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in non-targeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy-number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

Hammer et al. (Hammer RE et al. Cell 63 :1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rat demonstrated the most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in a widely different phenotypic response even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. The specification does not provide any guidance as to whether a given promoter used for expressing an exogenous gene in one animal would have been functional in other animals and even if the promoter may

have been active, whether the level of the transgenic product produced would have been sufficient to produce a certain phenotype. If not, what steps would have been take to address this issue?

Further, the art of recombinant protein production in the milk of transgenic animals is unpredictable. Mercier et al. (Transgenic Animals: Generation and Use Ed. Houdebine LM p 479, 1997) teach "much progress remains to be done before routinely using transgenesis for generating farm animals producing milk for non-therapeutic use. In the present state of the art, it is difficult to predict that a construct will be functional because of insufficient knowledge on gene transcript, pre-MRNA processing, RNA and protein stability. Integration of the microinjected transgene is aleatory resulting in highly variable levels of expression, and possible detrimental effects." (page 479, paragraph 4) For example a recent study by Palmer et al. (Transgenic Res 12(3):283-292, 2003) teach expression of recombinant human protein C in two lines of mice homozygous for the mouse whey acidic protein/human protein C transgene. The authors teach that both lines had normal growth, activity and fertility, but failed to lactate normally and were unable to raise litters. The authors concluded that "expression of rHPC induced a lactational phenotype that involves abnormal morphological, biochemical, and functional differentiation of mammary epithelial cells" and that the basis of this phenotype "may involve secondary, rather than primary, effects of rHPC on mammary gland development." Therefore, while expression of recombinant proteins driven by a mammary promoter is well known in the art, it is not predictable whether ALL proteins would be expressed, whether expression would be at a physiologically functional level,

and whether elevated expression of a recombinant protein could result in a pathological state. Additionally, generating transgenic animals having multiple transgenes driven by a mammary tissue promoter would need to address issues of detrimental effects on expression due to presence of dual or multiple transgenes, as well as these issues. Therefore, while the level of skill of an artisan practicing the claimed invention will be high, in view of the unpredictability of the state of the art of animal transgenesis in general as well as production of recombinant protein in milk of transgenic animals, an artisan would require specific guidance to carry out the full breadth of the claimed invention.

The instant specification provides a general disclosure of a method for expressing multiple recombinant proteins in the milk of transgenic non-human animals. The working example taught by the instant specification teaches specific guidance as to the production of human clotting factor IX and porcine lactoferrin in the milk of a transgenic porcine generated by the microinjection of a plasmid comprising both a hFIX and a porcine lactoferrin transgene driven by the bovine α lactalbumin promoter. The instant specification teaches the collection of milk of said porcine and quantitative and qualitative analysis of recombinant protein expression by dilution of said milk prior to Western Blot analysis using human cloning factor IX and porcine lactoferrin-specific antibodies. However, the instant specification does not provide specific guidance as to how to express any combination of more than a single recombinant protein, other than the combination of human clotting factor IX with porcine lactoferrin, located in separate plasmids, versus being located in the same plasmid, in the milk of any transgenic non-

human mammal, other than porcine. Whereas at the time of the invention, the state of the art of expressing recombinant protein in the milk of transgenic animals was well known and a skilled artisan was provided specific guidance in the art for using a plasmid having a transgene for a specific protein to be expressed in the milk of transgenic animals, expression of multiple proteins, whether on the same or different plasmids, was not predictable or well known in the art. Dyck et al. (Trends Biotech 21(9):394-399, 2003) teach, "another aspect to consider when producing proteins in the tissues of transgenic animals is the ability of the tissues to execute complex post-translational modifications. This process is different from protein to protein and might also vary from tissue to tissue." (page 396, paragraph 3) Therefore, whereas the full embodiment of the claimed invention is the production of any protein in the milk of a transgenic animal, in view of the lack of specific guidance provided by the instant specification and further in view of the unpredictability of the art of animal transgenesis and recombinant protein production in transgenic milk, a skilled artisan is only enabled for production of the combination of hFIX and porcine lactoferrin in the milk of a transgenic swine.

The claims also encompass a transgenic non-human mammal having cells expressing porcine lactoferrin wherein said lactoferrin acts as an immune modulator, which can help boost the immunity and resistance of nursing offspring, reducing their diarrhea and fighting inflammation. The instant specification does not provide specific guidance to produce any transgenic animal having cells comprising porcine lactoferrin transgenes in combination with a different transgene encoding a recombinant protein such that the milk of said mammal boosts immunity and resistance of nursing offspring.

At the time of the invention, it was known in the art that endogenous lactoferrin found in milk of humans, rats and porcine had immune stimulating properties. However, at the time of the invention, it was not known if porcine lactoferrin is effective cross-species. For example, would expression of exogenous porcine lactoferrin in rat milk act as an immune modulator for nursing offspring of said rat? Additionally, in view of the unpredictability of the art of transgenesis and further, the art of multi-gene transgenesis, a skilled artisan is not enabled to produce a transgenic non-human mammal such that porcine lactoferrin was expressed at high enough levels in combination with a different recombinant protein without specific guidance from the instance specification. Therefore, in view of the unpredictability of the art of transgenesis, specifically in terms of the variable level of transgene expression in transgenic animals, compounded with the unpredictability of multi-transgene expression in a transgenic animal, and the unpredictability of the use of porcine lactoferrin across species, it would take an undue burden of experimentation for a skilled artisan to produce a transgenic non-human mammal whose milk would act as an immune modulator in nursing offspring.

Further, whereas the instant specification teaches the detection and analysis of recombinant protein in diluted milk of said transgenic porcine, the instant specification provides no specific guidance as to how these proteins would be purified. Dyck et al. teach "the raw potential for producing valuable proteins with transgenic animals seems apparent. However, the purification of these proteins from their source, whether milk, eggs or semen, is still a hurdle to be overcome and creates, often undefined, regulatory issues. Isolation of recombinant proteins from milk is complicated by the presence of

micelles and fat globules." (page 396, paragraph 3) Therefore, because the art of animal trangenesis and expression of multiple recombinant proteins in the milk of a transgenic animal is highly unpredictable, without specific guidance provided by the inventor, a skilled artisan could not make and use the full embodiment of the claimed invention. Without specific guidance, a skilled artisan would have an undue burden of necessary excessive experimentation to produce any number of any recombinant proteins using multiple expression plasmids comprising only one transgene due to the unpredictability of the expression of multiple recombinant proteins in a transgenic animal. Without specific guidance from the instant specification, a skilled artisan would also have an undue burden of necessary experimentation to be able to isolate a functional protein from milk derived from a transgenic animal when more than one recombinant protein is being expressed in said milk.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the claimed invention is not enabled for its full breadth and limiting the scope of the claimed invention to a method for producing a transgenic swine whose somatic and germ cells comprise a transgene wherein said method comprises: (i) introducing (a) a plasmid comprising two transgenes, wherein said transgenes comprise DNA sequences encoding human clotting factor IX (hFIX) and porcine lactoferrin, respectively, wherein both transgenes are operably linked to a mammary gland specific promoter or (b) a 1:1 mixture of plasmids, one comprising a mammary gland specific promoter operably linked to a nucleic acid encoding hFIX, the other comprising a mammary specific promoter

operably linked to a nucleic acid encoding porcine lactoferrin into a swine embryo, (ii) transplanting said embryo comprising said plasmid or plasmids into a pseudopregnant swine, (iii) allowing the embryo to develop into a transgenic swine, wherein expression of said transgenes result in the production and secretion of hFIX and porcine lactoferrin in the mammary tissue of said swine, wherein the expression of recombinant porcine lactoferrin in said milk acts as an immune modulator in said swine; and said method further comprising collecting milk from said transgenic swine is proper.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 2, 4, 5, 6, 9, 10, 11, 14, 15, 16, 17, 18, 19, 21, 22, 23, 26, and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claims 1 and 3 recites "recombinant protein genes." The claim is indefinite because it is unclear in the instant specification as to what are the metes and bounds of the term "recombinant protein genes." The instant specification does not define what is encompassed by the term "recombinant protein genes."

5. Claims 1 and 15, step (a), recite the term "can express in mammary glands." The claim is indefinite because it is not clear as to what the term is referring to, the expression plasmid or the recombinant protein. Is the expression plasmid expressed in mammary glands or is the recombinant protein expression in mammary glands?

6. Claim 1 and 15, step (b), recite the term "transferring said expression plasmid." It is not clear where said expression plasmid is being transferred to. Further, the claim recites the phrases "plasmid that carries multiple recombinant protein genes" and "plasmid carrying multiple recombinant protein genes." An expression plasmid does not "carry" genes. Reciting "comprising" will be remedial.

7. Claims 1 and 15 recite the limitation "said transgenic mammal" in method step (b) of the claim. There is insufficient antecedent basis for this limitation in the claim. Whereas the preamble recites "transgenic non-human mammals," the term "transgenic mammal" is not previously recited elsewhere in the method.

8. Claims 2 and 16 recite the phrase "constructed on the same expression plasmid." The claims are indefinite and vague because it is not clear as to where on said plasmid said genes are located.

9. Claims 4 and 19 recites the limitation "the construct of said expression plasmid" in the claim. There is insufficient antecedent basis for this limitation in claims 4 and 19

or in the claims on which 4 and 19 depend, claims 1 and 15. Claims 1 and 15 recite only "expression plasmid", not "construct."

10. Claims 4 and 19 recite the phrase "capable of regulating recombinant protein genes" and "obtain continuous and stable gene expression" in reference to a "5' regulatory sequence." Whereas a regulatory sequence on its own can regulate tissue expression specificity, a regulatory sequences does not have the functional ability to regulate continuous and stable gene expression.

11. Claim 4 and 19 recite the terms "5' regulatory sequence" and "recombinant protein genes." It is necessary to use an article before these terms in order to meet with the grammatical standards of the English language.

12. Claims 4 and 19 recite the term "behind" in reference to location of transgenes. This term is unclear and the use of "operably linked" is remedial.

13. Claims 5 and 21 should recite "offspring" not "offsprings." Further, the term "sexual reproduction" is not generally used in claim language. Using the term "breeding" is remedial.

14. Claims 9 and 26 and recite the term "act as immune modulator" in reference to the "expression of exogenous porcine lactoferrin." It is not clear from the instant specification how expression of lactoferrin can effect immune modulation.

15. The term "90% of normal human plasma" in claims 10 and 22 is a relative term which renders the claims indefinite. The term "90%" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Since "normal" human plasma activity would vary between individuals, the metes and bounds of "90%" is not clear.

16. Claim 14, steps (c) and (d), recite the term "said milk" and "aforesaid milk," It is noted that claim 1 recites "milk of non-human mammal"; therefore claim 14 does not have proper antecedent basis for the terms "said milk" or "aforesaid milk." Recitation of "the milk of said non-human mammal" is recommended.

17. Claims 1, 2, 4, 5, 6, 9, 10, 11, 14, 15, 16, 17, 18, 19, 21, 22, 23, 26, and 27 are generally narrative and indefinite, failing to conform with current U.S. practice. They appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

Conclusion

18. No claim are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Norma C Alonzo whose telephone number is 571-272-2910. The examiner can normally be reached on 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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